# Annexin A1 and annexin A5 in cardiovascular disease

# Addendum III

## Valorization of this thesis

Valorization*, to assign a value to* this thesis is challenging. Knowledge valorization refers to "the process of crafting value from knowledge", by making knowledge suitable or available for social and/or economic use. This definition expects 'value' to be expressed as a direct impact on society or to be conveyed to a currency.

In my humble opinion, the primary drive for research should be curiosity rather than currency. This curiosity may or may not lead to economic gain, but should foremost expand scientific knowledge. Since we are part of a knowledge-based economy in which tax money and charities contribute to perform science, society should benefit from research one way or another. Increasing knowledge by itself does not directly impact society, but has major influence on future innovations. The principal objective of this thesis was to improve insights in the role of annexin A1 (anxA1) and annexin A5 (anxA5) in cardiovascular disease (CVD), which is the leading cause of death in the developed or in other words "wealthy" countries. It is therefore tempting to suggest that there must be both monetary and social 'value' somehow. For more information about the socio-economic impact that molecular imaging of CVD has, I would like to refer to the final part of chapter 2. The valorization of my thesis will focus on chapters 3 to 6, which contain the actual experimental research.

**Chapter 3** elaborates on the role of endogenous anxA5 in atherosclerosis and identified that anxA5 is involved in the clearance of death cells and therefore comprises a potential target for treatment. AnxA5 is a proven and widely used agent for *in vitro* and *in vivo* imaging of apoptosis, and forms the founding upon which MosaMedix BV and PharmaTarget BV are build. These companies offer jobs which is presently not a unnecessary luxury. Besides offering employment, the products improve diagnosis and treatment of disease. On Short-term, there is no economic or social value in this chapter. Additional research is needed to transform this target into actual therapy, but one could imagine anxA5 as target for mild inflammatory disorders, as is discussed in the clinical relevance part of the general discussion of this thesis.

**Chapter 4** and **chapter 5** investigate a potential therapeutic role of anxA1. We are the first and only group to produce this anti-inflammatory mature protein in sufficient amounts to test and validate efficacy in large-scale *in vivo* experiments. These results show great potential for anxA1 in treatment of inflammation related diseases and future research should elucidate whether anxA1 is a valuable addition to existing therapies. To

express the scientific findings of these chapters in monetary value; the price of purified human recombinant anxA1 from Abcam is just below €1500 for 100μg of protein. We are able to produce a small multiple of this amount with relatively minute costs in commodities and labor. Based on published data and personal correspondence we have equal or better purity, stability and efficacy. In addition to anxA1, we have used a very innovative approach to reduce the damage of neutrophils. In addition, we have generated a novel form of heparin without anticoagulant activity. This therapy aims to reduce the cytotoxicity of neutrophils based on its negative charge, and has already proven efficacy very recently in an animal model of sepsis. This new form of heparin is patented for the treatment of sepsis and would be the only known effective therapy for sepsis for the first 24 critical hours. Additional research is currently carried out to confirm efficacy and test potential use in the clinic. A new company is currently arising from the patent assigned to the new heparin.

**Chapter 6** focused on structural analysis of anxA1. Increasing the knowledge about structural properties of a protein paves avenues for augmentation in order to increase functionality. We have produced the protein triple isotopically labeled and analyzed the structure by nuclear magnetic resonance. In addition to novel structural insights of anxA1, the primary value of this chapter is the optimized strategy for the production of this protein. This strategy can be applied by other researchers for other proteins and therefore propel structural analysis studies and consequently novel drug development.

In conclusion, the findings in this thesis are in short term primary of value to other researchers, but in long term could be translated into commercially available products and/or services.